PPTA
Plasma Protein Therapeutics Association

Overview of Plasma Fractionation Practices

FDA's Plasma Standards Workshop

August 31, 2004

Mary Gustafson, Sr. Director, Global Regulatory Policy, PPTA

PPTA
Plasma Protein Therapeutics Association

History

- Plasma has been used as source material for plasma therapies since the discovery by Cohn of cold ethanol precipitation in the 1940's
- Plasma provided to fractionators under "short supply" agreements (i.e., contracts)
- Source Plasma licensed in the mid-1970's
- Recovered plasma still supplied under short supply

Plasma Collection/Storage Conditions

- Source Plasma
  - In U.S., minimum standards set by regulation:
    1. "Immediately after filling, . . .stored at a temperature not warmer than -20ºC, . . ."
    2. Shipping: "-5ºC or colder"
    3. Excursion allowance: ". . .one episode of storage temperature fluctuation that is warmer than -20ºC and colder than -5ºC for not more than 72 hours. . .provided that the plasma has been and remains frozen solid."
    4. Relabeling provision: ". . .inadvertently exposed. . .to a storage temperature warmer than -20ºC and colder than +10ºC may be issued only if labeled as 'Source Plasma Salvaged.'"
  - Additional criteria as specified by the fractionator
- Recovered Plasma
  - In U.S., few specific regulations/extrapolated from requirements for transfusible plasma
  - Criteria specified by the fractionator

Plasma Collection/Storage Conditions

- Recovered Plasma
  - In U.S., few specific regulations (labeling)
    1. Expiry: Collection date instead of expiration date
    2. Intended use: Caution: For Manufacturing Use Only
    3. Intended use: Caution: For Use in Manufacturing Noninjectable Products Only
    4. Intended use: Not for Use in Products Subject to License Under Section 351 of the Public Health Service Act
  - Other requirements extrapolated from whole blood and plasma for transfusion
  - Criteria specified by the fractionator

Plasma Collection/Storage Conditions

- Human Plasma for Fractionation/EU
  - One standard as specified in European Pharmacopoeia Monograph
  - For labile protein recovery, frozen by cooling rapidly at -30ºC or below as soon as possible and at the latest within 24 h of collection
  - For nonlabile proteins, plasma from whole blood frozen at -20ºC or below within 72 h of collection
  - Store frozen plasma at or below -20ºC
  - Shipping is same as storage
  - Excursion allowance: between -20ºC and -15ºC for not more than a total of 72 h without exceeding -15ºC on more than one occasion as long as the temperature is at all times -5ºC or lower

PPTA
Plasma Protein Therapeutics Association

Harmonization

- Plasma therapies manufacture/marketing is global
- PPTA supports and highly recommends harmonization
  - Harmonization is not conformance to the most stringent regional standard
  - Harmonization is based on scientific principles
  - In the absence of agreement on science, industry appreciates flexibility

PPTA
Plasma Protein Therapeutics Association

Recent Developments

- Consolidations / Divestitures
- Plasma Center Closures
  Fractionation Facility Closures
- Reduced Volume of Fractionated Plasma
- Staffing Reductions

PPTA
Plasma Protein Therapeutics Association

Recent Developments

- New Companies Entering Market
- New Product Approvals
- Facilities Upgrades and Build-outs
- Enhanced Technologies Resulting in Higher Yields
- Utilization of Both Source and Recovered Plasma

U.S. Plasma Collection Data

- In 2003, approximately 12.8 million liters of plasma collected for fractionation
  - 10.4 million liters Source Plasma
  - 2.4 million liters recovered plasma

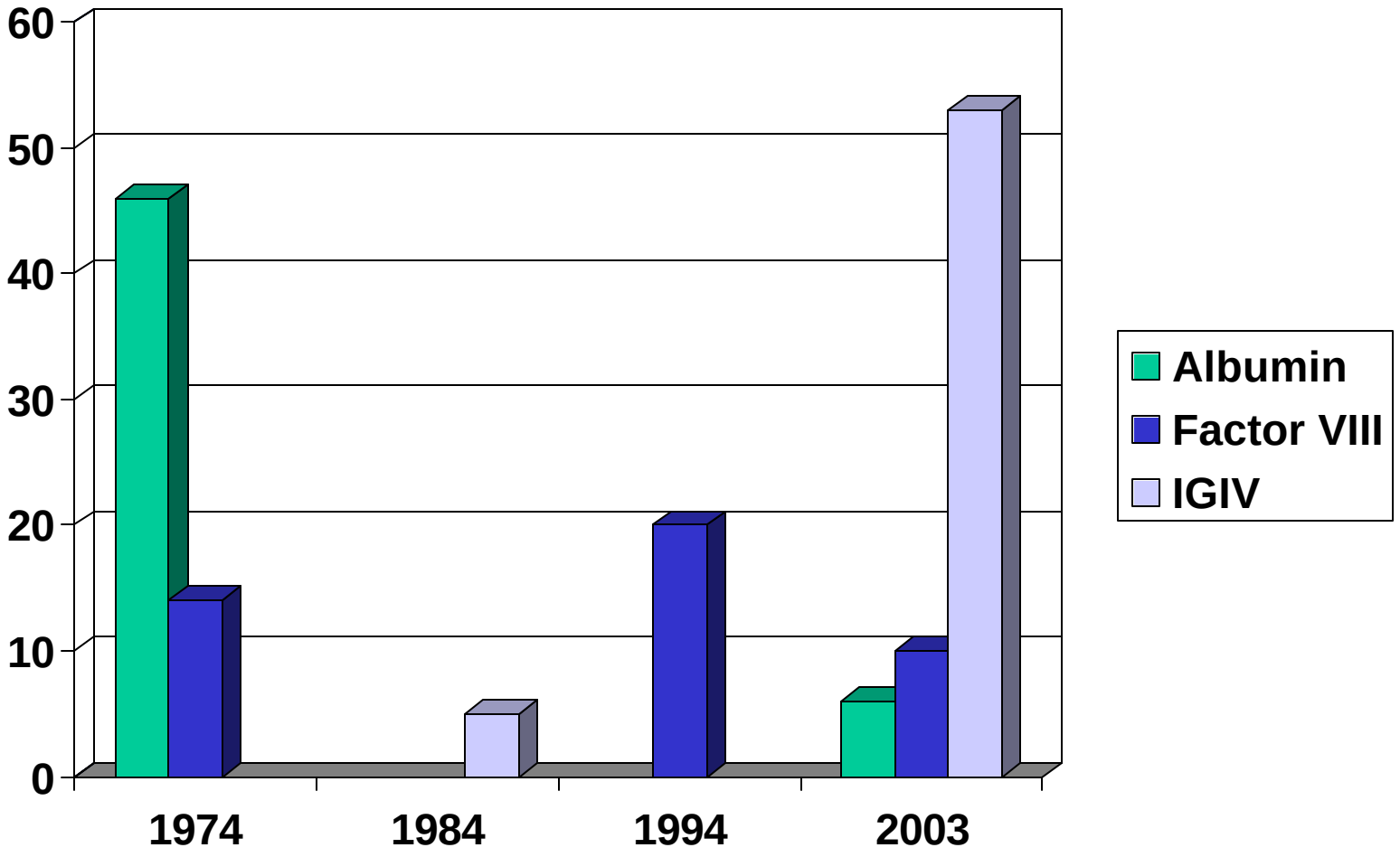
Source: The Marketing Research Bureau, Inc.

Plasma Economics

Drivers for plasma collection:

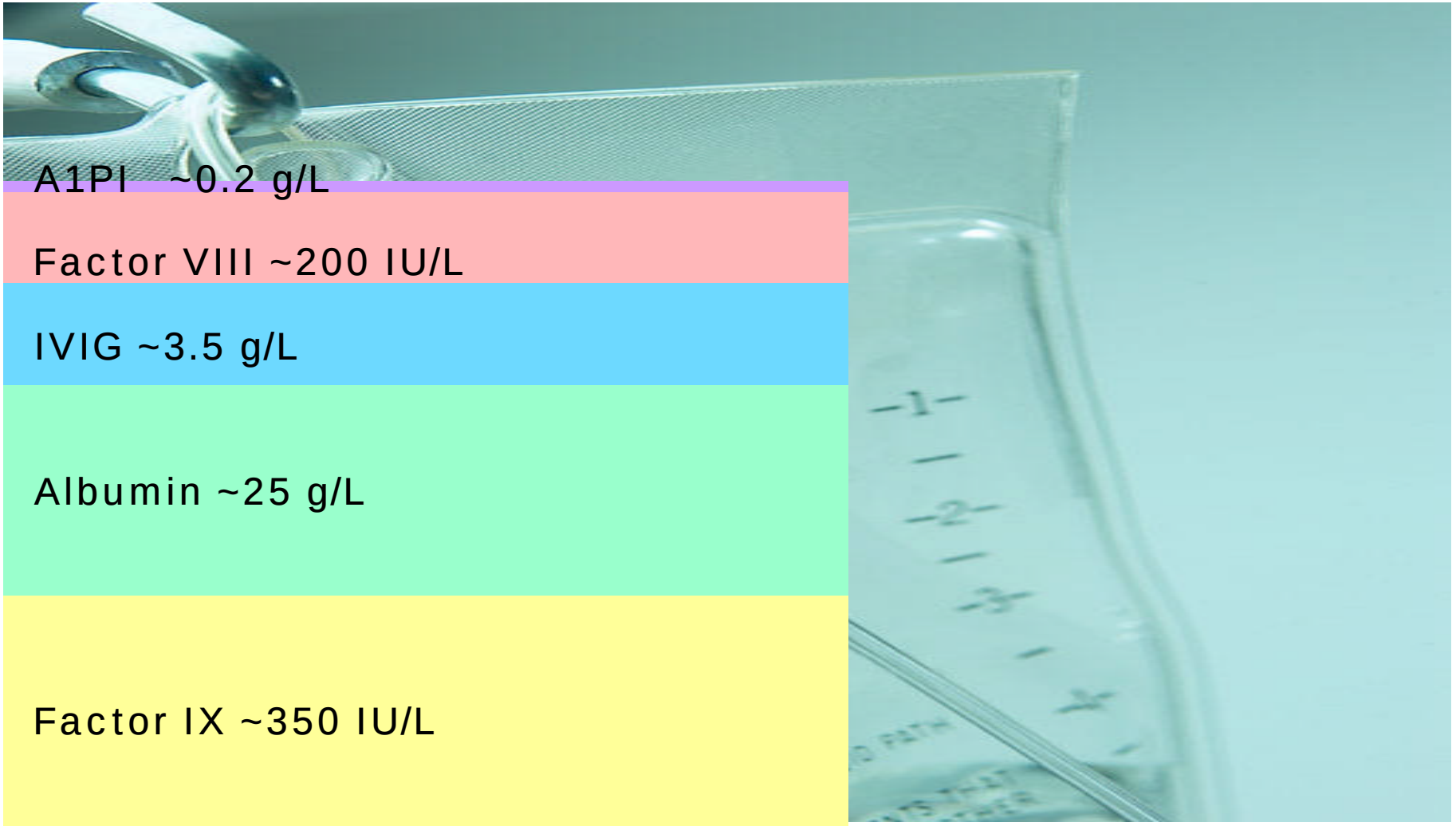
PPTA
Plasma Protein Therapeutics Association

Market Mix Over Time



Source: The Marketing Research Bureau, Inc.

Plasma Therapy Portfolio



*Industry-wide Estimates

Plasma Fractionation Variables

- Source Material
  - Donor issues: biologic variability; frequency of collection
  - Collection/processing issues: method of collection, bleed time, time to separation, time to freezing, freezing temperature, storage temperature, thaw/pooling conditions

- Manufacturing
  - Fractionation
  - Viral clearance
  - Purification
  - Concentration

PPTA
Plasma Protein Therapeutics Association

Summary

- Changes in product demand and industry business practices impact manufacturing, not volume of plasma collected
- Source and recovered plasma are both suitable starting materials
- Final product outcomes are dependent on a variety of factors
- Manufacturers validate processes based on influence of various factors